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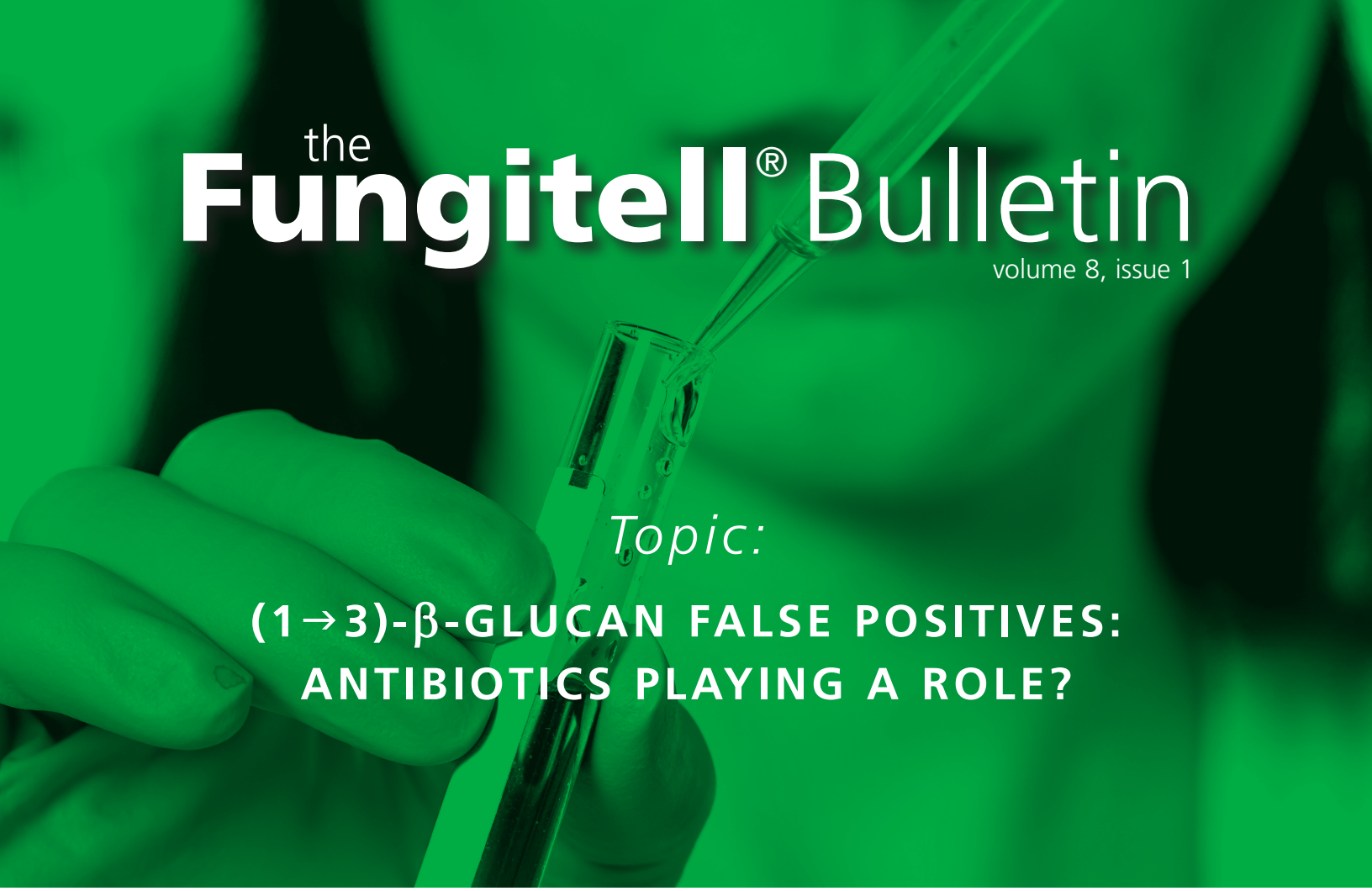

Topic:

(1→3)-β-GLUCAN FALSE POSITIVES: ANTIBIOTICS PLAYING A ROLE?

Discussion:

The utilization of serum (1→3)-β-glucan (BG) data in the clinical management of invasive fungal disease has become well established in routine clinical practice and is listed in research and practice guidelines (De Pauw, *et al.,* 2008; Cuenca-Estrella *et al.,* 2012). In the area of antimicrobial stewardship, the very high negative predictive value (NPV) of serum BG in allowing the safe withholding or early withdrawal of unneeded systemic antifungals has been extensively demonstrated (Prattes, *et al.,* 2014; Posteraro, *et al.,* 2016; Nucci, *et al.,* 2017; Rautemaa, *et al.,* 2017; Bansal, *et al.,* 2018). In the area of positive predictive value, however, positive serum BG titers need to be interpreted in light of the complete clinical picture, as iatrogenic contamination and intestinal translocation may contribute to elevated serum BG titers. For example, blood fractionation products are well known to cause serum BG diagnostic false positives (Buchacher *et al.,* 2010; Liss, *et al.,* 2016a; Held, *et al.,* 2011, Egger, *et al.,* 2018). In the area of iatrogenic contamination, the potential of contaminated antibacterials to generate false positives has been extensively addressed. As most in-patients, who are at highest risk for invasive fungal disease, are also receiving antibacterials for at least part of their hospitalization, it is worth reviewing the literature as regards the impact of antibiotics upon patient serum BG titers.

The question of whether antibacterials are associated with false positive (1→3)-β-glucan results has been addressed in both laboratory and clinical studies. Marty, *et al.,* (2006) looked at 44 antibacterials, addressing both the in-container, diluted for administration, and estimated post-administration dilution titers. While 5/44 tested positive (≥80 pg/ml) when reconstituted in-container, none would have been positive after post-administration dilution. More recently, Liss *et al.,* (2016b) addressed the same issue and examined 30 antibacterials and 5 antifungals. They observed that 20/30 antibacterials and 5/5 antifungls contained sufficient BG as to be able to meet or exceed the positive cutoff of 80 pg/ml. However, these in-container values did not allow for dilution upon administration, or clearance, which would have, essentially, eliminated the likelihood of positive circulatory titers (Finkelman, 2017). Nonetheless, their findings provide a cautionary note regarding iatrogenic contamination of patients with BG.

Data from numerous clinical studies looking at measures of diagnostic performance shed light on the question raised by potentially

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BG-contaminated antibiotics. Serum BG has a very high NPV in the vast majority of studies presenting such data. It is worth noting that the extremely high NPV of serum BG (Hammarstrom, *et al.,* 2015), would be very unlikely given that most patients being assessed for serum BG burdens, those at risk for invasive fungal disease, are also receiving antibiotics (Prattes, *et al.,* 2014; Posteraro, *et al.,* 2016; Nucci *et al.,* 2016; Rautemaa *et al.,* 2018; Bansal *et al.,* 2018). Clinical data on the issue of antibacterials-related diagnostic false positivity has been reported in a number of studies over the last one and a half decades (Racil, *et al.,* 2013; Metan, *et al.,* 2010, 2012 a,b; Desjardins, *et al.,* 2018; Furfaro, *et al.,* 2014; Albert *et al.,* 2011). Although elevated serum BG, without IFD, was observed in some patients, the preponderance of data shows that antibacterials are unlikely to be a significant source of diagnostic false positive serum BG titers.

In light of the lack of systematic evidence of antibiotic contribution of false positives, one must look at another source of elevated BG titers. Translocation of gut luminal material due to mucosal barrier injury (MBI) is an emerging field of study, with multiple markers of both intestinal epithelial cell damage and circulating luminal microbial molecules having been reported (Leelahavanichkul, *et al.,* 2016; Yang *et al.,* 2017; Hoenigl, *et al.,* 2016; Gonzalez, *et al.,* 2019; Mehraj, *et al.,* 2019). While still an emerging field, a rising stream of studies with observations of correlation between markers of MBI, microbial translocation, and systemic inflammation have been published over the last 20 years. Published pre-clinical animal model data as well as patient data demonstrate the correlation between MBI-related endotoxin and BG translocation and increased morbidity and mortality in multiple disease states (McIntyre, *et al.,* 2011, Hoenigl, *et al.,* 2018; Zhou, *et al.,* 2018). Accordingly, while an elevated BG may not always be explainable by a fungal infection, other patient health-related factors may be responsible and not iatrogenic contamination.

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